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Zaprinast, a type V phosphodiesterase inhibitor, dilates capacitance vessels in anaesthetised rats

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Abstract

The effects of zaprinast (a type V phosphodiesterase inhibitor) on mean arterial pressure, heart rate, cardiac output, mean circulatory filling pressure, arterial and venous resistances were compared to those of sodium nitroprusside in three groups, each of intact or ganglion-blocked, Inactin-anaesthetised rats. In intact rats, zaprinast (1.5, 3.0 mg kg^{-1} min^{-1}) and sodium nitroprusside (8.0, 64.0 μg kg^{-1} min^{-1}) dose-dependently reduced mean arterial pressure and arterial resistance, but did not alter cardiac output and venous resistance. Both increased heart rate, with the effect of zaprinast less than that of sodium nitroprusside. Mean circulatory filling pressure was elevated by both doses of zaprinast but only the high dose of sodium nitroprusside. In rats given mecamylamine (3.7 μmol kg^{-1}, i.v. bolus) and noradrenaline (7.3 nmol kg^{-1} min^{-1}), zaprinast and sodium nitroprusside elicited dose-dependent reductions in mean arterial pressure, arterial and venous resistances, and mean circulatory filling pressure. Both increased cardiac output, with the effect of zaprinast greater than that of sodium nitroprusside at the low dose. Zaprinast but not sodium nitroprusside reduced heart rate. Our results indicate that zaprinast, similar to sodium nitroprusside, dilates both resistance and capacitance vessels in ganglion-blocked rats infused with noradrenaline to restore vasomotor tone. Zaprinast but not sodium nitroprusside has a direct, negative chronotropic effect on the heart.

Keywords: Zaprinast; Phosphodiesterase, cGMP-selective; Circulatory filling pressure, mean; Arterial resistance; Venous resistance; Capacitance vessel

1. Introduction

It is well documented that the intracellular second messengers, cGMP and cAMP, play significant roles in the regulation of vascular smooth muscle tone. Elevations of cGMP and/or cAMP in vascular smooth muscle cells are associated with relaxation via the lowering of intracellular Ca^{2+} concentrations. The inhibition of cGMP and/or cAMP hydrolysis is therefore expected to promote vasodilatation. Phosphodiesterases represent a principle mechanism by which the actions of cGMP and cAMP are terminated. At least seven distinct families of phosphodiesterases are now known to exist in mammalian tissues. These phosphodiesterases exhibit tissue-specific distribution, and differential substrate specificity as well as regulatory properties. Among them, the type V phosphodiesterases metabolise only cGMP, and are calmodulin-independent. They are localised in vascular smooth muscle cells of a variety of arteries and veins of various species, including human, and inhibited by zaprinast (for review, see Polson and Strada, 1996).

In vitro studies have demonstrated that zaprinast increased the concentrations of cGMP but not cAMP in isolated rat (Lugnier et al., 1986) and rabbit (Ahn et al., 1989; Weishaar et al., 1990) aortae, attenuated phenylephrine-induced contractions of bovine intrapulmonary artery and vein (Ignarro et al., 1987), and caused relaxations of phenylephrine-precontracted rat and rabbit aortae (Martin et al., 1986) and dog saphenous vein (Villanueva et al., 1991), as well as prostaglandin $F_{2\alpha}$-precontracted porcine coronary artery (Merkel et al., 1992). Acute intravenous infusion of zaprinast into anaesthetised rats reduced blood pressure via the reduction of total peripheral resistance (Trapani et al., 1991; Dundore et al., 1992). Also, chronic administration of zaprinast reduced blood

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pressure in spontaneously hypertensive rats (McMahon et al., 1989).

Although the vascular effects of zaprinast have been extensively investigated, little is known about its actions on the venous circulation in vivo. To our knowledge, there are no published in vivo studies examining the effects of zaprinast on mean circulatory filling pressure and venous resistance. Mean circulatory filling pressure, an index of body venous tone (Guyton et al., 1973), is the pressure that would exist following circulatory arrest and instantaneous redistribution of blood throughout the circulation. Changes in mean circulatory filling pressure, at a constant blood volume, reflect predominantly alterations in venous tone (Rothe, 1993; Tabrizchi and Pang, 1992). Venous resistance, though lower than its arterial counterpart, is a major determinant of cardiac output due to low pressure in the venous circulation (Rothe, 1993; Pang, 1994). A decrease in venous resistance increases flow and facilitates venous return, which in turn, increases cardiac output.

The objectives of our investigation were to examine the effects of zaprinast on mean circulatory filling pressure and venous resistance in anaesthetised rats under basal condition and after ganglionic blockade with mecamylamine followed by elevation of venomotor tone with continuous infusion of noradrenaline (Pang, 1994). As a comparison, the cardiovascular profile of sodium nitroprusside was also studied under similar experimental conditions.

2. Materials and methods

2.1. Animal preparation

Male Sprague–Dawley rats (400–500 g) were anaesthetised with Inactin (100 mg kg^{-1} i.p.). Body temperature was maintained at 37 ± 1°C using a rectal probe and a heat lamp attached to a Thermistemp Temperature Controller (Model 71; Yellow Spring Instrument OH, USA). The left iliac artery was cannulated and connected to a pressure transducer (P23DB, Gould Statham, CA, USA) to record mean arterial pressure. Heart rate was derived electronically from the upstroke of the arterial pulse pressure by a Grass 7P4G tachograph. Polyethylene (PE50) cannulae were also implanted into the right iliac vein and the left external jugular vein for the administration of vehicle or drugs, the inferior vena cava via the left iliac vein for the measurement of central venous pressure by another pressure transducer (P23DB, Gould Statham). A saline-filled, balloon-tipped catheter was inserted through the right external jugular vein and positioned at the right atrium. The precise location of the balloon was verified by transiently inflating the balloon, which when correctly placed, caused a simultaneous decrease in mean arterial pressure to 20–25 mmHg and an increase in central venous pressure within 5 s of circulatory arrest. Mean arterial pressure, heart rate and central venous pressure were continuously monitored and recorded on a Grass Polygraph (Model RPS 7C8). Additional catheters were introduced into the left ventricle via the right carotid artery and the right iliac artery for the injection of radioactively-labelled microspheres and the withdrawal of a reference arterial blood sample (Wang et al., 1995), respectively. The rats were allowed 30 min to stabilise before baseline mean arterial pressure, heart rate, mean circulatory filling pressure and cardiac output were measured.

The method for determining mean circulatory filling pressure (MCFP) has been described elsewhere in detail (Tabrizchi and Pang, 1992; Wang et al., 1995). Briefly, plateau readings of mean arterial pressure and central venous pressure were noted at 4–5 s after inflation of the atrial balloon. To avoid rapid equilibration of arterial and venous pressures during circulatory arrest, the arterial pressure contributed by the small amount of trapped arterial blood was corrected by the following equation: $MCFP = VPP + 1/60(FAP - VPP)$, where FAP and VPP denote the final arterial pressure and venous plateau pressure, respectively, and $1/60$ represents the ratio of arterial to venous compliance.

2.2. Measurement of cardiac output

A well-stirred suspension (100 μl) containing 20 000–25 000 ^{57}Co-labelled microspheres (15 μm diameter; Du Pont Canada, Ont., Canada) was injected and flushed over 10 s into the left ventricle at the end of the 30 min equilibration period and 10 min after the intravenous infusion of a drug or vehicle. A blood sample was withdrawn (Harvard infusion/withdrawal pump) 10 s before the injection of each set of microspheres from the right iliac arterial catheter into a heparinised saline-filled syringe at 0.35 ml min^{-1} for 45 s. The blood was slowly injected back to the rats immediately after the counting of radioactivity at 80–160 keV using a 1185 Series Dual Channel Automatic Gamma Counter (Nuclear-Chicago, IL, USA) with a 3-in. NaI crystal.

2.3. Experimental protocol

Rats were randomly divided into six groups ($n = 6$ each). Immediately after baseline measurements of cardiovascular variables, three groups of rats were infused with the vehicle (0.05 N NaOH), zaprinast (ED_{40} and ED_{80} doses, 1.5 and 3.0 mg kg^{-1} min^{-1} or 5.5 and 11.0 μmol kg^{-1} min^{-1}, respectively) and sodium nitroprusside (ED_{40} and ED_{80} doses, 8.0 and 64.0 μg kg^{-1} min^{-1} or 0.03 and 0.22 μmol kg^{-1} min^{-1}) for 12 min each dose. ED_{40} and ED_{80} doses were chosen with reference to our preliminary results in intact, Inactin-anaesthetised rats under similar experimental conditions (data not shown), and represented

the doses of zaprinast or sodium nitroprusside which caused 40% and 80% of decrease in mean arterial pressure, respectively. Cardiac output followed by mean circulatory filling pressure measurements were taken 10 min after the infusion of a drug or vehicle, at the plateau phase of response to each drug. A recovery period of 12 min, during which infusion was stopped, was allowed between doses. The effects of vehicle, zaprinast and sodium nitroprusside on haemodynamic parameters were also studied in another three groups of rats given i.v. bolus mecamylamine (3.7 μmol kg^{-1}) followed by continuous infusion of noradrenaline (7.3 nmol kg^{-1} min^{-1}) to elevate vasomotor tone. The dose of mecamylamine used was found to block ganglionic transmission effectively for more than 2 h (Wang and Pang, 1991).

2.4. Drugs

Zaprinast was a gift from Sanofi Recherche (France). Inactin was obtained from Research Biochemicals (MA, USA). Mecamylamine powder and noradrenaline hydrochloride were purchased from Aldrich (WI, USA). Sodium nitroprusside was obtained from Fisher Scientific (NJ, USA). All drugs were dissolved in normal saline (0.9% NaCl) except for zaprinast, which was dissolved in 0.05 M NaOH.

2.5. Calculations and data analysis

Cardiac output (CO, ml min^{-1}), arterial resistance (R_a, mmHg min ml^{-1}) and venous resistance (R_v, mmHg min ml^{-1}) were calculated according to the following equations:

$$\mathrm{CO} = \frac{\text{rate of withdrawal of blood} \times \text{total injected cpm}}{\text{cpm in withdrawn blood}}$$

$$R_a = \frac{\mathrm{MAP}}{\mathrm{CO}}$$

$$R_v = \frac{\mathrm{MCFP} - \mathrm{CVP}}{\mathrm{CO}}$$

Due to the technical difficulty of monitoring right atrial pressure in small animals, central venous pressure was used in place of right atrial pressure to estimate pressure gradient to venous return (MCFP − right atrial pressure). This is legitimate as mean central venous pressure is nearly identical to mean right atrial pressure (Rothe, 1993).

All data are expressed as mean ± S.E.M. Comparisons were made with analysis of variance (ANOVA) followed by Duncan's multiple range test at $P < 0.05$ as the level of statistical significance.

3. Results

3.1. Intact rats

Baseline values of mean arterial pressure, heart rate, cardiac output, mean circulatory filling pressure, arterial and venous resistances among the six groups of rats were not significantly different from each other (Table 1). The vehicle (time-control) did not cause significant changes in any haemodynamic parameters (Fig. 1). The ED_{40} and ED_{80} doses of zaprinast and sodium nitroprusside caused similar dose-dependent reductions of mean arterial pressure and arterial resistance (Fig. 1). Both drugs increased heart rate, with the tachycardic effects of zaprinast less than those of sodium nitroprusside, but did not significantly alter cardiac output and venous resistance relative to the corresponding readings in the time-control group. Mean circulatory filling pressure was increased by both doses of zaprinast but only the high dose of sodium nitroprusside.

3.2. Ganglion-blocked rats

Injections of mecamylamine into three other groups of rats caused similar reductions of mean arterial pressure, heart rate, cardiac output and mean circulatory filling pressure but insignificant changes in arterial and venous resistances (Table 1). The subsequent infusion of noradrenaline caused similar increases in mean arterial pressure, heart rate, mean circulatory filling pressure, arterial

Table 1
Pooled values (mean ± S.E.M.) of baseline haemodynamic parameters in intact rats ($n = 18$) and rats treated with i.v. bolus injections of mecamylamine (mec) followed by i.v. infusion of noradrenaline (NA) ($n = 18$)

	MAP (mmHg)	HR (beats min^{-1})	CO (ml min^{-1})	MCFP (mmHg)	Ra (mmHg min ml^{-1})	Rv (mmHg min ml^{-1})
Intact rats						
baseline	94 ± 2	355 ± 10	96 ± 6	4.3 ± 0.1	1.00 ± 0.05	0.035 ± 0.002
Ganglion-blocked rats						
baseline	95 ± 2	358 ± 9	102 ± 5	4.2 ± 0.1	0.95 ± 0.05	0.031 ± 0.001
mec	74 ± 3[a]	328 ± 8[a]	80 ± 8[a]	3.5 ± 0.1[a]	0.97 ± 0.09	0.033 ± 0.003
NA	122 ± 4[a,b]	419 ± 9[a,b]	82 ± 4[a]	5.6 ± 0.2[a,b]	1.50 ± 0.10[a,b]	0.057 ± 0.004[a,b]

[a]Significantly different ($P < 0.05$) from the corresponding baseline readings prior to any drug treatment.
[b]Significantly different ($P < 0.05$) from the corresponding readings after mec injections.

and venous resistances but did not alter cardiac output in all groups (Table 1). Relative to the respective baselines, the combination of ganglionic blockade and noradrenaline increased mean arterial pressure, heart rate, mean circulatory filling pressure, arterial and venous resistances but reduced cardiac output.

In ganglion-blocked rats, the vehicle did not significantly alter any haemodynamic readings but tended to increase heart rate, arterial and venous resistances, and decrease cardiac output with the passage of time (Fig. 2). Both doses of zaprinast and sodium nitroprusside caused greater ($P < 0.05$) dose-dependent reductions in mean arterial pressure relative to the changes in intact rats, with the depressor responses to zaprinast slightly greater than those to sodium nitroprusside. Heart rate was dose-dependently decreased by zaprinast, but unaltered by sodium nitroprusside. Both drugs caused dose-dependent reductions in arterial and venous resistances. The low doses, but not the high doses, of zaprinast and sodium nitroprusside caused similar reductions in mean circulatory filling pressure. Zaprinast and sodium nitroprusside also increased cardiac output; cardiac output response to the low dose of zaprinast was greater than that to sodium nitroprusside.

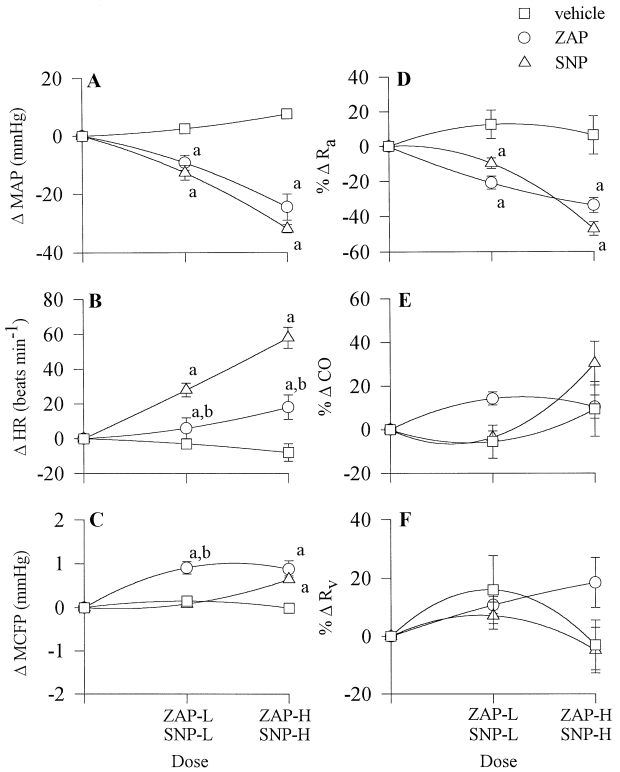

Fig. 1. Effects (mean ± S.E.M.) of i.v. infusion of zaprinast (1.5 and 3.0 mg kg^{-1} min^{-1} shown as ZAP-L and ZAP-H, respectively), sodium nitroprusside (8.0 and 64.0 μg kg^{-1} min^{-1} as SNP-L and SNP-H, respectively) or equivalent volumes of vehicle (0.05 M NaOH) on mean arterial pressure (MAP, A), heart rate (HR, B), mean circulatory filling pressure (MCFP, C), arterial resistance (R_a, D), cardiac output (CO, E) and venous resistance (R_v, F) in three groups of intact rats ($n = 6$ each). All measurements were obtained 10 min after the infusion of a drug or vehicle. [a]Significantly different ($P < 0.05$) from the corresponding values in the vehicle group. [b]Significantly different ($P < 0.05$) from the corresponding values in the SNP group.

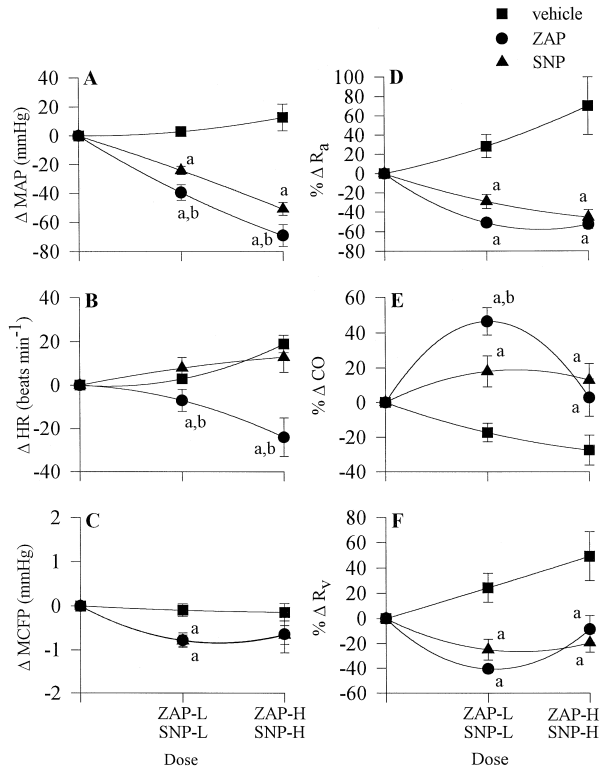

Fig. 2. Effects (mean ± S.E.M.) of i.v. infusion of zaprinast (1.5 and 3.0 mg kg^{-1} min^{-1} shown as ZAP-L and ZAP-H, respectively), sodium nitroprusside (8.0 and 64.0 μg kg^{-1} min^{-1} as SNP-L and SNP-H, respectively) or equivalent volumes of vehicle (0.05 M NaOH) on mean arterial pressure (MAP, A), heart rate (HR, B), mean circulatory filling pressure (MCFP, C), arterial resistance (R_a, D), cardiac output (CO, E) and venous resistance (R_v, F) in three groups of rats ($n = 6$ each) pretreated with mecamylamine (3.7 μmol kg^{-1}) and continuously infused with noradrenaline (7.3 nmol kg^{-1} min^{-1}). All measurements were obtained 10 min after the infusion of a drug or vehicle. [a]Significantly different ($P < 0.05$) from the corresponding values in the vehicle group. [b]Significantly different ($P < 0.05$) from the corresponding values in the SNP group.

4. Discussion

Our results show that the ED_{40} and ED_{80} doses of zaprinast and sodium nitroprusside caused similar dose-dependent reductions in mean arterial pressure and arterial resistance in intact rats. Both drugs reduced mean arterial pressure by decreasing arterial resistance, since cardiac output readings were unchanged. As expected with vasodilator drugs (Pang, 1994), both caused greater depressor responses following the impediment of autonomic reflexes with mecamylamine and the elevation of vasomotor tone with intravenous infusion of noradrenaline. The hypotensive responses of zaprinast were slightly greater than those of sodium nitroprusside. Hypotensive responses to both

were also due to reduced arteriolar resistance, since cardiac output readings were not reduced.

Zaprinast elicited lesser tachycardia than did sodium nitroprusside in intact rats. The tachycardic responses to sodium nitroprusside were eliminated by ganglionic blockade indicating that the heart rate responses were due to hypotension-induced reflex activation of the sympathetic nervous system. In contrast to sodium nitroprusside, zaprinast reduced heart rate following ganglionic blockade suggesting that the drug is negatively chronotropic. Direct negative chronotropism may explain why equihypotensive doses of zaprinast caused less tachycardia than did sodium nitroprusside in intact rats. Zaprinast has been shown to reduce heart rate in overdrive pacing-induced myocardial ischaemia in conscious rabbits (Szilvassy et al., 1993).

Neither zaprinast nor sodium nitroprusside reduced mean circulatory filling pressure or venous resistance in intact rats. Mean circulatory filling pressure was significantly elevated by both doses of zaprinast and the high dose of sodium nitroprusside. Following ganglionic blockade, zaprinast as well as sodium nitroprusside similarly reduced mean circulatory filling pressure and venous resistance suggesting dilatation of the capacitance vessels. High doses of both zaprinast and sodium nitroprusside did not lower mean circulatory filling pressure and venous resistance further suggesting that maximum reductions of the two parameters have been achieved at the low doses. These observations indicate that the zaprinast- and sodium nitroprusside-induced increases in mean circulatory filling pressure in intact rats were due to hypotension-induced reflex venoconstriction. We have previously shown that endogenous sympathetic tone has to be abolished in order to reveal the venodilator activity of hypotensive drugs such as verapamil (Waite et al., 1988), nitroglycerin (D'Oyley et al., 1989), hexamethonium (D'Oyley and Pang, 1990) and calcitonin gene-related peptide (Abdelrahman and Pang, 1992). It should be noted that not all vasodilator agents reduce mean circulatory filling pressure. Hydralazine caused a steep rise in mean circulatory filling pressure in intact rats and no change in mean circulatory filling pressure in ganglion-blocked rats (D'Oyley et al., 1989) suggesting its lack of venodilator action. Pinacidil, a potassium channel opener, did not reduce mean circulatory filling pressure or venous resistance in intact or ganglion-blocked rats (Waite et al., 1988). The results from this study show that in ganglion-blocked rats with elevated vasomotor tone, zaprinast has similar vasodilator activity as sodium nitroprusside in resistance and capacitance vessels.

Cardiac output was not altered by either zaprinast or sodium nitroprusside in intact rats. In areflex rats, both doses of zaprinast and sodium nitroprusside increased cardiac output; zaprinast at the low dose caused markedly greater increment of cardiac output than did sodium nitroprusside. The increases in cardiac output elicited by both drugs were likely due to reductions in flow resistance, arterial and venous resistances, thereby facilitating venous return. The greater increase in cardiac output (despite bradycardia which should reduce cardiac output) caused by the low dose of zaprinast relative to sodium nitroprusside was likely secondary to the greater, though insignificant, reductions in arterial and venous resistances elicited by zaprinast. The lesser increase in cardiac output at the high dose of zaprinast was probably due to the lesser decrement in venous resistance.

Trapani et al. (1991) reported that intravenous infusion of zaprinast (1 and 2 mg min^{-1} kg^{-1}) reduced mean arterial pressure and total peripheral resistance in anaesthetised, intact rats, as well as rats with autonomic blockade via intravenous bolus injections of atropine and propranolol. However, in contrast to our results on cardiac output and heart rate, zaprinast (1 and 2 mg min^{-1} kg^{-1}) increased cardiac output but did not alter heart rate in intact rats, and increased cardiac output as well as heart rate in areflex rats. These discrepancies could be attributed to the differential experimental conditions in the two studies. The acute placement of an electromagnetic flow probe around the ascending aorta for the measurement of cardiac output in the Trapani study required more invasive surgery than the surgical procedure needed for the injection of microspheres in our study. Furthermore, the methods of autonomic blockade were also different between the two studies.

Our results show that zaprinast is a dilator of both resistance and capacitance vessels in vivo. Its arterial and venous dilator efficacies are comparable to those of sodium nitroprusside which is one of the most efficacious vasodilator agents known. It is of interest that zaprinast was reported to reverse nitroglycerin-induced tolerance (Pagani et al., 1993; De Garavilla et al., 1996) and protect the heart against pacing-induced myocardial ischaemia (Szilvassy et al., 1993). The vascular profile of zaprinast and other members of phosphodiesterase type V inhibitors should be investigated in cardiovascular diseased states.

We conclude that zaprinast dose-dependently reduced mean arterial pressure and arterial resistance in both anaesthetised intact and areflex rats. Zaprinast did not alter venous resistance and cardiac output, and slightly increased heart rate and mean circulatory filling pressure in intact rats. In areflex rats, zaprinast significantly decreased mean circulatory filling pressure, venous resistance as well as heart rate. The vasodilator activity of zaprinast is similar to that of sodium nitroprusside.

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